REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. Status of the claims

Claims 1-4 and 7-9 were previously canceled without disclaimer or prejudice thereof.

Claims 5 is currently amended to recite "wherein the encoded polypeptide renders endogenous wild-type Flk-1 unresponsive to VEGF." Exemplary support can be found throughout the specification, for example at paragraph [0033] of the specification as published, U.S. Publication No. 2005/0107321.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Because the foregoing amendment does not introduce new matter, entry and examination thereof by the Examiner is respectfully requested. After amending the claims as set forth above, claims 5 and 6 are now pending in this application.

II. Claim rejection – obviousness-type double patenting

Claims 5-6 are rejected for obviousness-type double patenting as allegedly being unpatentable over claims 1-9 of U.S. Patent No. 5,851,999. Specifically, the Office Action asserts that "a person of ordinary skill in the art would immediately grasp, upon reading the patented claims, the desirability of making a cell line as currently claimed to produce the viral particles used in the patented pharmaceutical composition." (Office Action at page 3). As such, the Office Action concludes, the present claims are obvious. Applicants respectfully traverse the rejection for at least the reasons provided below.

A. The proposed modification would change the principle of operation of the pharmaceutical composition

Claims 1-9 of the '999 Patent relate to a pharmaceutical composition comprising an expression vector encoding a truncated FLK-1 polypeptide, and a pharmaceutically acceptable carrier. A pharmaceutical composition comprising an expression vector would have a different principle of operation than a pharmaceutical composition including a cell line. For example, a pharmaceutical composition comprising an expression vector would be administered to a patient, (likely targeted to a specific cell population) for uptake by the patient's cells. Once within the targeted cell population, the encoded truncated polypeptide would be expressed *within* these specific cells. The cells expressing the truncated polypeptide would exhibit the dominant negative phenotype (*e.g.*, inhibit the cellular effects of VEGF binding). In contrast, if a foreign cell line expressing FLK-1 was administered to a patient, the foreign cell line would express the polypeptide outside the target cells. The patient cells would have to somehow "uptake" the truncated polypeptide to illicit the dominant negative affect (*i.e.*, inhibit the cellular effects of VEGF binding). Thus, the principle of operation of the pharmaceutical composition would be changed.

B. A cell line is not an obvious variant or modification of a pharmaceutical composition.

Contrary to the Office Action assertions, one skilled in the art would not find a cell line comprising a recombinant vector to be obvious in light of a pharmaceutical composition comprising an expression vector and a pharmaceutically acceptable carrier. First, a pharmaceutical composition comprising an expression vector and a pharmaceutically acceptable carrier is clearly intended for administration to a patient. A cell line comprising a recombinant vector may not be intended for administration to a patient.

Second, it is possible that administration of a cell line (as opposed to the pharmaceutical composition) could be harmful to the patient and may not yield therapeutic results. For example, it is likely that administering a foreign cell line would illicit an immune response from the patient. If the patient is suffering from cancer and has undergone chemotherapy, chances are that the patient's immune system is already weakened. Challenging the patient by administering foreign cells would likely cause the patient to

become even weaker. Moreover, a cell line administered to a patient may not even express, or be capable of expressing, the truncated polypeptide after administration. Thus, one of ordinary skill and creativity would not consider a cell line including a recombinant vector obvious in light of a pharmaceutical composition comprising an expression vector and a pharmaceutically acceptable carrier.

Accordingly, for at least these reasons, reconsideration and withdrawal of the obviousness-type double patenting rejection is respectfully requested.

III. Claim rejection – 35 U.S.C. § 103(a)

Claims 5-6 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,185,438 ("Lemischka"), Matthews *et al.*, PNAS 88:9026 (1991), and Terman *et al.*, BBRC 187:1579 (1992), in view of Ullrich *et al.*, Cell 61:203 (1990), and Ueno *et al.* (Science 252: 844, Ueno-1 and JBC 267:1470, Ueno-2). To summarize the obviousness rejection, the Office asserts that:

1) the sequence of the Flk-1 receptor was known (Matthews and Lemishka references);

2) that Flk-1 function as a VEGF receptor was known (Treman reference);

3) the effects of the deletion of the kinase domain of certain other receptor tyrosine kinase was known (PDGFR, FGFR1, EGFR) (Ueno and Ullrich references). These "other receptors" form dimers. If one member of the dimer pair is missing the intracellular domain (*i.e.*, the kinase domain), then the dimer no longer functions in signal transduction (*see e.g.*, Office Action at page 5);

4) Flk-1 allegedly shares structural and functional homology to the "other receptors" (*see e.g.*, Office Action at page 6); and

5) therefore, making a deletion mutant of the kinase domain of Flk-1 would be obvious, and the effects of that deletion (*i.e.*, dominant negative inhibition of cellular effects of VEGF binding) would be predictable (*see e.g.*, Office Action at page 5-7).

Applicants respectfully traverse this ground for rejection for at least the following reasons.

A. None of the cited references disclose that Flk-1 functions as a dimer; accordingly, activity of a Flk-1 mutant can not be predicted based on the activity of kinase receptor dimer mutants

The Office asserts that the mutant activity of the claimed polypeptide (amino acids 1-806 of SEQ ID NO: 2) would have been predictable in light of the teachings of the cited reference, particularly in light of the Ullrich and Ueno references. According to the Office Action, both references teach that if one member of a kinase receptor *dimer* is kinase deficient, dominant negative inhibition occurs (*i.e.*, the *dimer* can not function as a kinase). The Office Action asserts it would have been obvious not only to make the claimed truncated polypeptides, but also to predict the function of the truncated polypeptides (*i.e.*, dominant negative inhibition of VEGF signaling). For example, in support, the Office asserts the following:

> [Because] Flk-1 is the murine homolog of the KDR receptor disclosed by Terman et al....it would be desirable *to investigate the dimeric combinations* in which the receptor occurs, and the relationship of such to the physiological responses known to occur in response to the ligand.... (Office Action at page 5, emphasis added).
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> Ullrich teaches that kinase deficient growth factor receptors are expected to be signaling incompetent, and the Ueno teachings that truncated FGFR1 and PDGF-beta receptors lacking portions of their cytoplasmic domains had dominant negative signaling activity, i.e., *when combined with a "normal" subunit to form a dimer*, were incapable of signaling. (Office Action at page 5, emphasis added).
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> [A]s stated in the previous rejection, the remaining cited references (including two articles by Ueno) are all drawn to examples in which tyrosine kinase receptors are structurally related to the Flk-1 receptor were altered within the cytoplasmic domain, resulting in *proteins that formed signaling incompetent dimers, with dominant-negative characteristics*. (Office Action at page 6, emphasis added)
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> Ullrich...[teaches] that although normal in its binding characteristics, the kinase-negative mutant of the EGF receptor was unable to stimulate calcium influx....One does not have to thoroughly understand the entire biology system to have an expectation that *deletion of the intracellular domain would*

result in signaling incompetent dimers. (Office Action at page 6, emphasis added).

The Office Action continues, asserting that because Flk-1 is the homolog of KDR, Flk-1 should have the same function as KDR, and that a "truncated Flk-1 would be expected to inhibit angiogenesis (as taught by Terman), as such would be signaling incompetent (Office Action dated 9-19-08 at page 5).

Applicants respectfully point out that while Terman teaches that Flk-1 and KDR are likely homologues, Terman does not teach truncated polypeptides or angiogenesis inhibition, and that none of the cited references, alone or in combination, teach the claimed truncation mutant, namely amino acids 1-806 of SEQ ID NO: 2.

Applicants also respectfully point out that *none* of the cited references teach that Flk-1 (or KDR) function as dimers. In fact, Terman states that ***"[i]t is not known*** whether KDR and *flt* can form functionally active dimers analogous to the PDGF receptor dimers" and "***it is not known*** whether KDR, *flt* or heterodimer KDR/*flt* mediates mitogenic activity and/or vascular permeability." (Terman at page 1585).

Thus, Applicants respectfully disagree with the Office Action assertions that one skilled in the art would find it obvious to make the truncated mutants, "investigate *the dimeric combinations* in which the receptor occurs", and to expect the claimed truncated polypeptide "to render endogenous wild-type Flk-1 unresponsive to VEGF and inhibit the cellular effects of VEGF binding." Applicants respectfully contend that, for the claimed Flk-1 sequence, dominant negative inhibition of cellular effects of VEGF binding *would not have been obvious* to a skilled artisan. Specifically, one of ordinary skill and creativity would not have expected the claimed polypeptide to "render endogenous wild-type Flk-1 unresponsive to VEGF" as recited in the claims *because Flk-1 was not know to function as a dimer*.

Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

B. Because *flt* was a known VEGF receptor with high affinity for VEGF, it was unexpected that the *flk-1* mutant would inhibit the cellular effects of VEGF binding

In addition, it was entirely unexpected that the truncated Flk-1 variant would have an inhibitory effect on the cellular response of VEGF. Such results were unexpected because at least one other receptor, *flt*, was known to bind VEGF with high affinity.[1] It also was known that *flt* is expressed in endothelial cells of a growing tumor.[2] Significantly, *flt* has a 50-fold higher affinity for VEGF than Flk-1.[3] Given the importance of VEGF signaling in angiogenesis during *inter alia*, development, wound healing and organ regeneration, some redundancy in the system would be expected. Consequently, the skilled artisan would not have expected that blocking the Flk-1 signaling pathway would shut down the cellular response to VEGF, resulting in suppression of angiogenesis and inhibition of tumor growth. Rather, one of ordinary skill in the art would have anticipated that the biological response to VEGF, such as the proliferation of blood vessels, would still be transduced through *flt* or some as yet undiscovered receptors.

For at least these reason, the ability of the claimed truncated Flk-1 receptor proteins to inhibit angiogenesis were unexpected. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

IV. Conclusion

The present application is in condition for allowance. Favorable reconsideration of the application is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected

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[1] *See e.g.,* Terman et al., BBRC 187:1579 (1992).

[2] *See*, Plate *et al.*, 1992, Nature 359: 845-848; Plate *et al.*, 1993, Cancer research 53: 5822-5827. (Ref. A35)

[3] *See*, Waltenberger *et al.*, 1994, J. Biol. Chem. 269: 26988-26995.

or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date: March 18, 2009

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